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(57) Abstract

An oral delivery vehicle includes an aspected particle including a pharmaceutically active component and excipients, wherein the vehicle is formulated and/or constructed and arranged to provide controlled delivery of the pharmaceutically active component. The aspected particle possesses one dimension that is about an order of magnitude smaller than the other two dimensions. The vehicle may further contain a lubricious coating to improve mouth-feel. The vehicle may further contain a coating to provide sustained drug delivery to the particle.

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ASPECTED PARTICLES FOR ORAL DELIVERY

This application claims priority under 37 C.F.R. §119(e) to co-pending application U.S.S.N 60/069,501 filed December 15, 1997, "Oral Delivery Formulations", and to co-pending application U.S.S.N 60/095,283 filed August 4, 1998, entitled "Aspected Microparticles for Oral Delivery", the contents of which are incorporated herein in their entirety.

Field of Invention

This invention relates to controlled-release pharmaceutical compositions in a aspected geometry dosage form for the administration of drugs.

Background of the Invention

Current orally delivered drugs are formulated in either solid (i.e., tablet, capsule or granules) or liquid (i.e., solution, suspension or emulsion) form. Solid dosage forms are conventionally the dosage forms of choice as they are typically more stable, less expensive to manufacture and have achieved general acceptance by consumers. The manufacture of solid dosage forms typically involves the processing of the drug with suitable excipients in order to produce a freely flowing powder. The type of processing and excipients chosen to manufacture the powder can be altered to provide desired effects such as controlled release of the drug. Once processed, the powder can be directly packaged into sachets, compressed into tablets or filled into capsules. Tablets can further be coated in order to improve palatability or provide controlled release of the drug.

The pediatric population and those who experience difficulty in swallowing primarily use liquid dosage forms. Liquid dosage forms are available orally as solutions, suspensions or emulsions. These liquids often contain colorants and flavorings in an attempt to increase palatability and patient acceptance.

Over 35% of the population are unable to adequately ingest either solid or liquid dosage forms due to physical limitations that include difficulty in swallowing due to esophageal dehydration, "mouth breathing", esophageal lesions or consumption

of anticholinergic medications. Geriatric patients also experience difficulty in chewing due to reduced bulk and tone of oral musculature as well as loss of or degradation in the quality of teeth.

In order to overcome this inability to tolerate solid dosage forms, health care providers typically crush solid dosage forms and disperse them in a semi-solid medium (e.g., applesauce, pudding, etc.). However, when tablets or capsules are tampered with the drug release kinetics of the pharmaceutics are altered. This results in dosing times and concentrations that are sub-optimal. Therefore, pharmaceutical manufacturers provide many drugs with the instructions: "DO NOT CRUSH" (*Hospital Pharmacy*, 21(1), 27, **1996**)

Fast dissolving tablets are available as an alternative to pill dosage formats. The tablets are retained in the mouth and rapidly dissolve to release the drug. Limitations to this method include restriction to drugs which do not have unacceptably unpleasant or bitter taste and the immediate release of the drug which prevents sustained release.

A further factor in patient drug non-compliance is the aesthetic response of the patient to the dosage format. When the "mouth-feel" of the dose is unpleasant, the patient is less likely to comply with the dosage regimen. The term mouth-feel is related to the type of sensation or touch that a dosage form produces in the mouth upon ingestion and is not concerned with the chemical stimulation of olfactory nerves or taste buds. However for the formulation to be successful, the overall effect in the mouth is important. In general, gritty or gummy textures are undesirable. A smooth texture is preferred. *See,* Pharmaceutical Dosage Forms; Edited by Leiberman, H.A. and Lachman, L. Marcel Dekker, Inc. New York, Volume I, pp. 291.

Currently available are free flowing particulant drug platforms in the form of rounded spheres which are currently marked under the tradenames Spoon Dose™ (Fuisz) and Pharmazome™ (Elan). The powders are added directly to food or drinks by the user just prior to ingestion. While such a drug delivery mechanism may be attractive to those wishing to avoid pills, the particles still retains their sense of grittiness and provides an unacceptable mouth-feel to the user.

In attempts to address some of the above issues, different formulations have been investigated. Formulations of nano- or macrogranulars have been reported in US

5,618,527. In order to prevent the sensation of grittiness US 5,618,527 describes formulations in either liquid or tablet form consisting of spherical particles of not greater then 125 μm in diameter. Additionally, the particles are required to have smooth edges. These requirements severely limit the flexibility of the drug delivery of the drug.

An alternative attempt to reduce the sensation of grittiness by using a blend of a gritty drug product with a seedy fruit, such as strawberries, was described in US 5,102,664. In this combination, the seedy fibrous fruit texture masks the grittiness of the drug.

Flake-like geometries have been used to improve patient compliance in the administration of dosage formats. Peters *et al.* in US 4,581,232 describes the use of a flake-like structure for the microencapsulation of drugs in order to produce a suitable taste-masking effect for bitter after-taste medications. While the flake-format reduced patient aversion to the medication, the flake format yielded rapid bioavailability. Thus, this formulation was an unstable format for controlled drug delivery.

There is a need for controlled-release formulations for pharmaceutical administrations that are easy to ingest; have a time-dependent release that offset the short half-life of the active ingredient and thus minimize multiple dosages; exhibit satisfactory stability; and are sufficiently palatable and convenient to administer and that possess the appropriate mouth feel to ensure patient compliance. These and other limitations of the prior art are met in the present invention.

Summary of the Invention

It is an object of the invention to provide an oral drug delivery platform that is easy to ingest and retain and that does not possess the limitations of prior art solid and liquid form dosages. It is a further object of the invention to provide a drug delivery format that is spoon feedable.

It is a further object of the present invention to provide an alternative drug dosage format to the pill or capsule format.

It is a further object of invention to provide a drug delivery vehicle with enhanced mouth feel for increased patient compliance. It is a further object of the invention to provide a drug delivery vehicle with an acceptable organoleptic-feel.

The term organoleptic-feel is related to the stimulating any of the organs of sensation (PDR Medical Dictionary, Medical Economics, Montvale, NJ, 1995).

It is still a further object of the invention to provide a dosage form that is easy to ingest, and that provides a reservoir for controlled delivery of the drug.

These and other objects of the invention are achieved by the drug delivery platforms of the invention.

The present invention provides an oral delivery platform which overcomes the noncompliance issues in the geriatric and other patient populations and which optimizes the absorption of drugs.

The present invention provides a sustained delivery vehicle. The vehicle includes a pharmaceutically active component and other pharmaceutical acceptable excipients. The vehicle is flat or of an aspected morphology which provides an acceptable mouth feel. By aspected morphology, as that term is used herein, it is meant that at least one dimension of the vehicle is considerably smaller than the scale of the largest dimension. The smallest dimension may be one order of magnitude smaller than the largest dimension and may be up to three orders of magnitude (1000-fold) smaller. The vehicle is formulated and/or constructed and arranged to provide controlled delivery of the pharmaceutically active component to the desired site within the patient.

The aspected particles may be administered to the patient as a free-flowing powder. Alternatively, the aspected particles may be incorporated into a viscous base having a consistency capable of being spoon-fed. The viscous base may be food or non-food, such as by way of example, applesauce or cellulosic gel. The aspected particles optionally may be provided premixed with the base or it may be supplied separately from the base for mixing just prior to consumption. A delivery vehicle comprised of aspected particles including a pharmaceutically active component may be added to or mixed into the viscous base. The vehicle is flat of an aspected morphology which provides an acceptable mouth feel, while the viscous base facilitates swallowing and masks the presence of the drug. The vehicle may be formulated and/or constructed and arranged to instant release or to provide controlled delivery of the pharmaceutically active component to the desired site within the patient.

Use of highly aspected particles as a drug delivery vehicle provides significant benefits in controlling the release kinetics of a drug. Aspected particles provide uniform surfaces for drug diffusion and release over time. In addition, aspected particles experience a much less dramatic change in volume/surface area ratio as the particles dissolve, as compared to spherical particles. Where the volume/surface area ratio remains relatively constant, drug delivery vehicle architecture and design is simplified. Highly aspected particles for use in drug delivery vehicles may incorporate features known to be effective in the controlled release of drugs. For example, the release kinetics of the drug may be controlled by incorporation of hydrophobic or water-insoluble excipients to the aspected particle in order to retard drug dissolution. Similarly, coating the aspected particle with hydrophobic or water-insoluble polymeric films provides controlled drug release. Incorporation of the appropriate excipients into the aspected drug delivery vehicle provides controlled release kinetics

In one embodiment of the invention, the particles are coated to enhance mouth-feel. The particles may be coated with a fast swellable hydrogel, which results in enhanced palatability and mouth feel upon wetting. In another embodiment of the invention, the drug-incorporated aspected particles may be coated with a suitable film-former polymer or hydrogel that eliminates the damage to the epithelial cells of the esophagus additionally to enhancing the mouth-feel.

In one aspect of the invention, the drug delivery vehicle is are provided in a flat morphology. The drug-incorporated aspected particles may be administered in a variety of media, including liquid, tablet and food-feedable bases. The aspected particles are formulated to provide all the benefits for controlling the release kinetics of the drug as described herein.

An additional feature of the invention is that the flat morphology of the particles eliminates or reduces any unpleasant organoleptic sensations. The aspected particles are coated with a gel which forms a waterlike environment surrounding the particle. The mouth does not "see" the particle and no sensory reaction occurs.

The drug delivery vehicle and the spoon-feedable drug delivery vehicle described herein overcome the limitations of the prior art in providing a dosage format that is easy to administer, provides controlled drug release kinetics and

improves patient compliance. An further advantage of the present invention, includes increased ease of manufacturing and processing control. This alleviates of many of the shortcomings of nano- and macro-granules in terms of particle size and manufacturing constraints when dealing with spherical particles.

Brief Description of the Drawing

This invention is described with reference to the Figures, which are presented for the purpose of illustration only and which are in not limiting of the invention and in which:

Figure 1 is a schematic illustration of an aspected particle demonstrating the difference between flat particle dissolution and spherical particle in terms of constant surface/ volume ratio;

Figure 2 is a cross-sectional view of a hydrogel coated aspected particle that swells upon contact with water;

Figure 3 is a schematic illustration of multilayers aspected particles in which 3A illustrates drug layers in center layer "sandwiched" between two layers which do not contain drug but control the mouth-feel and the release rate; and 7B illustrates three different layers which may or may not contain drug.

Figure 4 is a cross-sectional view of an aspected particle having a core containing the pharmaceutically active agent and a film forming coating to control diffusion and release of the drug;

Figure 5 is a schematic illustration of a aspected particulates having a core of swellable hydrogel, drug and an outer membrane in which the swellable hydrogel core assists to push the drug from the aspected particle out in a controlled fashioned through the coating;

Detailed Description of the Invention

The present invention provides a novel oral drug delivery platform. The drug delivery vehicle may be advantageous in the administration of drugs to patients who experience difficulties in swallowing and/or tolerating medication in pills or tablets form. According to the invention, the drug may be incorporated into aspected particles that can be directly administered to the patient or that can be introduced

into foods, aqueous liquids or semi-solid bases to form a spoon-able or drinkable drug delivery system. The aspected particle may be readily administered to a patient to provide rapid or sustained drug delivery without leaving an undesirable organoleptic feel.

It has been observed previously that spherical or granular particulates leave an undesirable mouth-feel. The present invention has recognized that drugs that are incorporated into aspected particles possess enhanced mouth-feel by eliminating or reducing the gritty feel in the mouth. Because the flat morphology has a better mouth feel than current spherical delivery vehicles, e.g., U.S. 5,516,537, it is anticipated that they will be better tolerated by the patient, leading to more complete dosages and higher compliance.

The present invention also recognizes that oral dosage forms containing pharmaceutically active substances that are apportioned into many individual units, here the aspected particle of the invention, are more reliable in their biopharmaceutical behavior. Upon ingestion the particles spread over a large section of the intestinal tract and provide a improved uptake of the released drug. Also, the movement and quantity of the digestive fluids do not noticeably influence multiparticulate dosage forms, owing to the large number of individual particles that compensate for each other. Therefore, bioavailability is more reliable in such multiparticulate form than in monolithic dosage forms.

The aspected particle of the present invention, used as a drug delivery vehicle, includes pharmaceutical active or drug and a synthetic polymer or naturally occurring material which is compatible with the drug. The particle has an aspected pseudo-two dimensional morphology. By aspected morphology, as that term is used herein, it is meant that at least one dimension of the vehicle is considerably smaller than the scale of the largest dimension.

Figure 1 illustrates a highly aspected particle of the invention. An aspected particle **10** is formulated to include a desired pharmaceutic agent. It may further include a base and suitable excipients to provide desired properties, such as stability. The particle **10** is aspected, by which it is meant, that the particle has at least one dimension which is much smaller than the largest dimension of the particle. The smallest dimension may be one order of magnitude smaller than the largest

dimension and may be up to three orders of magnitude (1000-fold) smaller. The thickness of the aspected particle typically is the dimension which is smaller than the width or length. Typically the width to thickness ratio is in the range of 3:1 to about 1000:1. In preferred embodiments, the particle is about 100 nm to about 10 mm along the longest dimension.

The particle may be a substantially flat, thin layer, and thus possesses one dimension that is substantially less than the other two dimensions. The particle may be substantially planar or somewhat curvilinear. It may have an uneven surface, such as breakfast cereal flake. The particles are preferably free flowing and are of relatively uniform and consistent size and morphology.

The particle also includes pharmaceutically acceptable excipients to aid in the preparation of a stable pharmaceutical composition. Excipients include additives which have no therapeutic effect but which provide a desirable attribute to the drug delivery vehicle. Pharmaceutically acceptable excipients are well known and understood by those skilled in the art. Exemplary excipients include antioxidants, fillers, buffers, antibiotics, flavoring, colorants, adhesives, binders and the like. In particular, the pharmaceutically active compound may be incorporated into a natural or synthetic base or filler with which it is compatible. Suitable fillers include cellulosics, poloxamers and polyethyleneglycols.

The aspected nature of the particle according to the invention provides a reduced organo-leptic sensation; however, the particles may be further modified to improve mouth-feel.

In one aspect of the invention, the aspected particle is coated with a lubricious layer. The lubricious layer is slippery to the touch which facilitates the swallowing of the particles. An additional advantage of the hydrogel-coated particle is that the low friction surface reduces damage to the epithelial cells of the esophagus in addition to enhancing mouth-feel. The lubricious coating may be a hydrophobic or hydrophilic coating. Materials suitable for hydrophobic coating includes oils, such as silicone oils or siloxanes, and other low friction materials. Materials suitable for hydrophilic coatings include hydrogel polymer which become hydrated and swell in contact with an aqueous medium. The lubricious layer may contain flavorings and colorants for further enhancement of consumer appeal.

In preferred embodiments, the aspected particles of the invention are coated with an appropriate hydrogel. The hydrogel-coated particle swells upon contact with water to provide a smooth sensation and texture that enhances the mouth-feel and allows as easy as possible swallowing. Figure 2 demonstrates a hydrogel-coated, highly aspected particle **20** of the invention. A flat or aspected particle **10** is formulated, as in Figure 1, to include a desired pharmaceutic agent. The particle **10** may be coated with a gel coating **22**. Upon exposure to moisture, for example, in the mouth or other body cavities, the coating swells to give a lubricious, slippery coating. Exemplary hydrogels include, by way of example only, polyvinylpyrrolidone, polyvinyl alcohols, poly(N-vinyl lactams), polyethylene oxides, polyvinyl ethers, poly(acrylic acids) and derivatives thereof.

The aspected particles may be dispersed in an aqueous carrier substantially immediately prior to administration. The aspected particles are thereby combined with one or more gelling or swelling agents capable of forming a viscous medium around the particles in an aqueous carrier as well as being provided with a masking surface layer when dispersed in the aqueous carrier. This serves to mask uneven surfaces on the aspected particles and prevent them from adhering to oral mucosa when the composition is ingested and thus makes it easier to administer large dosages of an active substance. The masking surface layer is preferably provided by an increased viscosity of the viscous medium in the immediate vicinity of the particles relative to the viscosity of the surrounding aqueous carrier. A ready-to-use composition is prepared by mixing the composition with an aqueous carrier substantially immediately prior to administration of the composition.

In another aspect of the invention, the aspected particle of the invention is formulated to provide a desired kinetics of drug release. The particle may be designed for instantaneous release or for sustained release over periods of hours to days. The particle may be designed for linear (zero or first order), or non-linear drug release kinetics. The aspected morphology provides certain advantages over a spherical particle in drug release kinetics. The release kinetics from a spherically shaped delivery system is highly dependent on the surface area to volume ratio of the sphere. This ratio is highly dependent on the size distribution of the spheres. In contrast, with flat morphology the surface area to volume ratio is essentially

independent of the size. This is demonstrated in Figure 1, which shows the relatively constant surface area for an aspected particle **20** as it dissolves. Surface area changes as a function of the square of the particle dimensions in a pseudo-rectangular or disc-like particle, such as the aspected particle **20.** This is compared to the dramatic change in surface area spherical particle **22**, which is a cubed relationship. The surface area of a sphere changes as a cubic function of the radius. This in turn means more precisely controlled release kinetics. See, Ron and Langer (Chapter 4) and Gupta and Robinson (Chapter 6) in *Treatise on Controlled Drug Delivery Fundamentals, Optimization, Applications;* Edited by Agis Kydonieus, Marcel Dekker, Inc., New York, **1991**; for additional information, which is hereby incorporated by reference.

Selection of the appropriate additives or excipients also effects controlled drug delivery. Additionally, the particle may contain inert excipients to control drug stability and dissolution rates. Incorporating hydrophobic and/or water insoluble polymers in the system will impede the rate of water penetration into the system and therefor will slow down the dissolution rate of the drug. Thus, the release rate is controlled, in part, by the relative solubilities of the drug and base excipients. For example, for a water soluble drug, one may choose a water-insoluble base to retard the release rate of the drug. Similarly, for a water-soluble drug one may select a water-insoluble base to retard delivery.

Exemplary excipients for this purpose include polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, agar, carrageenan, xanthan, polyethylene glycol, a copolymer of acrylic and methacrylic acid esters, ethylcellulose, cellulose acetate, cellulose acetate phthalate, poly(methyl methacrylate), poly(methyl acrylate), polyethylene, polypropylene, poly(ethylene oxide), PET, poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethane, pectin, furcellaran, starch, zein, gelatin, collagen, polygeline, alginic acid, propylene glycol alginate or sodium alginate. One embodiment of the invention utilizes a matrix layer of a water soluble or swellable polymers, such as hydroxypropyl cellulose (e.g., 40-95% by weight and having a molecular weight above 100,000) and a homopolymer of ethylene oxide (e.g., 5-60 wt% and having a molecular weight from 3,000,000 to 5,000,000), a

water-insoluble polymer selected from the group consisting of ethyl cellulose, propyl cellulose, polyethylene and polypropylene (0-10wt%) and 2-10% of a plasticizer for controlled drug delivery.

The use of specific polymeric and hydrogel coatings allows engineering of drug products capable of being delivered to a patient in a relatively targeted fashion. In one embodiment, a drug product can be enteric coated so that the drug product will pass through the stomach into the intestine prior to initiation of release. Suitable coatings include ethylcellulose, polyvinylchloride, methylcellulose, polyurethane, cellulose acetate, polycarbonate, polyethylene, polypropylene, shellac and polymers of acrylic and methacrylic acids and esters of it.

The particle may be coated with one or more coatings, and the coatings may be the same or different, all to obtain the desired release kinetics. Interested readers are directed to the Hand Book of Pharmaceutical (2nd Edition., A. Wade & P.J. Welker, Eds., American Pharmaceutical Assoc., Washington, D.C. 1994) for further detail, which is hereby incorporated by reference. Alternatively, the particle can be designed to give a predetermined sustained release profile (i.e., zero or first order release kinetics) from moment of ingestion. The appropriate materials for use as the delivery vehicle will be readily apparent to one skilled in the art.

The aspected particles of the invention may be incorporated into a bolus system (e.g., a sugar tablet permeated with the active to be delivered), which is formulated for immediate dissolution and release in the mouth. Such systems are used in place of swallowable tablets for those patients that can not tolerate tablets. The disadvantage of this system is that it is not possible to achieve sustained delivery. However, the aspected particle of the present invention which has been formulated for sustained drug delivery may be incorporated into a bolus system to achieve controlled drug release. Thus, the sugar tablet is taken into the mouth by the patient where it dissolves, releasing the aspected drug-incorporated aspected particles of the invention. The aspected particles are then swallowed by the patient. The particles are non-gritty and have an acceptable mouth feel so that the patient can swallow them without a gagging reflex or unpleasant feeling in the mouth.

In other preferred embodiments, hydrogel coatings may be used to provide a controlled release of the drug. Hydrogel coatings may be used to coat the outer

surface of the aspected particle. Thus, the gel provides a physical barrier to diffusion of the drug, which slowly swells with water from the physiological environment. The water swollen coating permits drug diffusion. Where it is desired that the release rate be relatively slower, the hydrogel may be selected to be slow swelling. Conversely, where it is desired that the release rate be relatively faster, the hydrogel may be selected to be rapidly swelling. In yet another embodiment of the invention, the particle is coated with a rapidly swelling hydrogel. The rapid swelling and volume change of the coating is effective to disintegrate the particle, thereby providing substantially immediate drug delivery. Hydrogels having the above-noted swelling properties are well-know in the art.

These hydrogel coatings may be the same or different from those used as lubricious coatings described hereinabove. Thus, in one embodiment of the invention a single hydrogel layer is included which provides both a diffusion barrier for controlled drug delivery and a lubricious coating for improved mouth feel. In other embodiments of the invention, an inner coating is applied to control drug diffusion and an outer coating is used as the lubricious coating.

In other embodiments, a porosigen may be included in the coating, which is water-soluble and which dissolves in water to generate pores in the membrane to permit the release of the drug from the core in an aqueous environment. The porosigen may be selected from the group consisting of polyvinyl alcohol, polyvinylpyrrolidone, polyethyleneglycol, lactose, fumaric acid, citric acid, tartaric acid, sodium citrate, sodium bicarbonate, sodium fumarate, sodium carbonate, monosaccharides and disaccharides, hydroxypropylmethylcellulose, microcrystaline cellulose, polymers of acrylic and methacrylic acids, esters of polyurethane or polyvinylchloride, and potassium or sodium chlodires.

In other embodiments, an additive may be included in the coating which is enzymatically degradable and will degrade to generate pores in the membrane to permit the release of the drug from the core in the appropriate site at the gastrointestinal tract. The additive may be selected from compounds containing azo bonds, which will degrade in the lower gastrointestinal tract, (e.g., colon) in the presence of azo-reductase. Therefore the release will initiate only at the colon. For example, pectin is a suitable compound.

In another aspect of the invention, the drug is incorporated into the particle as a solid dispersion. The solid dispersion may also include acid or base components in order to control the pH for optimal drug dissolution rates. Exemplary acid components include adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid, and base components include calcium carbonate, calcium hydroxide, magnesium hydroxide, sodium bicarbonate, sodium carbonate, sodium citrate and sodium hydroxide. The solid dispersion may include a surfactant component selected from sodium lauryl sulphate, a sodium carboxylate, an alkyl sulphate, a polyethylene glycol ester, a polyethylene ether, an ethoxylated sorbitan ester and an alkyl trimethylammonium halide and mixes.

A drug product formulated in this manner has the following advantages: it is easy to ingest; as it is likely to stick into interstitial cavities of the mouth and as a result will not leave a residual sensation as spherical-shaped products do; it is relatively uniform in flow and handling characteristics for consumer appeal and ease of manufacturing; it possesses a controllable surface area to volume ratio to provide reproducible dissolution/release property compared with spherically shaped particles; it provides a controlled release kinetics that offset the short half-life of the active ingredient and thus does not require multiple dosages; it exhibits satisfactory stability; and it is sufficiently palatable and convenient, and has and acceptable mouth feel so as to ensure greater patient compliance over other current spherical-shaped products.

In another aspect of the invention, the particle may be incorporated into a semi-solid base to form a spoon-able drug delivery system. The semi-solid base may be comprised of pectin, guar gum, xanthan gum, gum arabic, gum acacia, locust bean gum, carageenan gum, alginic acid, psyllium hydrocolloid, oat bran gum, rice bran gum, glucomannan, tragacanth gum, karaya gum, tapioca, corn starch, cellulose gums, agar, gelatin, polyacrylates, polysaccharides, polyvinylpyrrolidone, pyrrolidones, polyols, collagen, polyethylene glycols, polyvinyl alcohols, polyethers, polyesters, natural or synthetic oils, liquid paraffin, beeswax, silicon waxes, natural or modified fatty acids, or combinations of thereof. Additionally viscous fruit purees such as apple, prune, apricot, pear, pineapple, banana, grape, strawberry, raspberry, blackberry, boysenberry, loganberry, dewberry, gooseberry, cranberry, mulberry,

elderberry, blueberry, fig, currant, kiwi may be used.

The invention may be applied to populations which experience difficulties in taking conventional solid and liquid dosage formats. For example, geriatric, pediatric, oncology patients or other patients who cannot swallow will benefit from a spoonable drug delivery dosage form. Similarly to the elderly, young children who cannot handle the swallowing of a tablet prefer a dosage form that could be spoon-fed to them. Cancer patients who undergo radiation therapy of the head and neck area or take chemotherapeutic drugs experience the lack of formation of saliva and/or esophagatits, which result in inability to take solid food such as tablets.

The active compounds that may be loaded into the drug delivery platforms of the present invention are any substances having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof.

Examples of biologically active compounds that might be utilized in a delivery application of the invention include literally any hydrophilic or hydrophobic biologically active compound. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use by the appropriate governmental agency or body. For example, drugs for human use listed by the FDA under 21 C.F.R. 330.5, 331 through 361; 440-460; drugs for veterinary use listed by the FDA under 21 C.F.R. 500-582, incorporated herein by reference, are all considered acceptable for use in the present invention.

The term "biologically active compound" includes pharmacologically active substances that produce a local or systemic effect in animals, plants, or viruses. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and conditions in an animal, plant, or virus. The term "animal" used herein is taken to mean mammals, such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, mice; birds; reptiles; fish; insects; arachnids; protists (e.g. protozoa); and prokaryotic bacteria. The term "plant" means higher plants (angiosperms, gymnosperms), fungi, and prokaryotic blue-green "algae" (i.e. cyanobacteria).

The pharmaceutically active compound may be any substance having

biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof. The term "protein" is art-recognized and for purposes of this invention also encompasses peptides. The proteins or peptides may be any biologically active protein or peptide, naturally occurring or synthetic.

Examples of proteins include antibodies, enzymes, steroids, growth hormone and growth hormone-releasing hormone, gonadotropin-releasing hormone, and its agonist and antagonist analogues, somatostatin and its analogues, gonadotropins such as luteinizing hormone and follicle-stimulating hormone, peptide-T, thyrocalcitonin, parathyroid hormone, glucagon, vasopressin, oxytocin, angiotensin I and II, bradykinin, kallidin, adrenocorticotropic hormone, thyroid stimulating hormone, insulin, glucagon and the numerous analogues and congeners of the foregoing molecules.

Classes of pharmaceutically active compounds include, but are not limited to, anti-AIDS substances, anti-cancer substances, antibiotics, immunosuppressants (e.g. cyclosporine) anti-viral substances, enzyme inhibitors, neurotoxins, opioids, hypnotics, antihistamines, lubricants tranquilizers, anti-convulsants, muscle relaxants and anti-Parkinson substances, anti-spasmodics and muscle contractants, miotics and anti-cholinergics, anti-glaucoma compounds, anti-parasite and/or anti-protozoal compounds, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents such as NSAIDs, local anesthetics, ophthalmics, prostaglandins, anti-depressants, anti-psychotic substances, anti-emetics, imaging agents, specific targeting agents, neurotransmitters, proteins, cell response modifiers, and vaccines.

A more complete listing of classes of compounds suitable for loading into polymers using the present methods may be found in the Pharmazeutische Wirkstoffe (Von Kleemann et al. (eds) Stuttgart/New York, 1987, incorporated herein by reference). Examples of particular pharmaceutically active substances are presented below:

Anti-AIDS substances are substances used to treat or prevent Autoimmune Deficiency Syndrome (AIDS). Examples of such substances include CD4, 3'-azido-3'-deoxythymidine (AZT), 9-(2-hydroxyethoxymethyl)-guanine acyclovir(), phosphonoformic acid, 1-adamantanamine, peptide T, and 2',3' dideoxycytidine.

Anti-cancer substances are substances used to treat or prevent cancer. Examples of such substances include methotrexate, cisplatin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, melphalan, uracil mustard, chlorambucil, busulfan, carmustine, lomusline, dacarbazine (DTIC: dimethyltriazenomidazolecarboxamide), methotrexate, fluorouracil, 5-fluorouracil, cytarabine, cytosine arabinoxide, mercaptopurine, 6-mercaptopurine, thioguanine.

Antibiotics are art recognized and are substances which inhibit the growth of or kill microorganisms. Antibiotics can be produced synthetically or by microorganisms. Examples of antibiotics include penicillin, tetracycline, chloramphenicol, minocycline, doxycycline, vanomycin, bacitracin, kanamycin, neomycin, gentamycin, erythromicin and cephalosporins.

Anti-viral agents are substances capable of destroying or suppressing the replication of viruses. Examples of anti-viral agents include a-methyl-P-adamantane methylamine, 1,-D-ribofuranosyl-1,2,4-triazole-3 carboxamide, 9-[2-hydroxy-ethoxy]methylguanine, adamantanamine, 5-iodo-2'-deoxyuridine, trifluorothymidine, interferon, and adenine arabinoside.

Enzyme inhibitors are substances which inhibit an enzymatic reaction. Examples of enzyme inhibitors include edrophonium chloride, N-methylphysostigmine, neostigmine bromide, physostigmine sulfate, tacrine HCl, tacrine,1-hydroxy maleate, iodotubercidin, p-bromotetramisole, 10-(alpha-diethylaminopropionyl)- phenothiazine hydrochloride, calmidazolium chloride, hemicholinium-3, 3,5-dinitrocatechol, diacylglycerol kinase inhibitor I, diacylglycerol kinase inhibitor II, 3-phenylpropargylamine, N6-monomethyl-L-arginine acetate, carbidopa, 3-hydroxybenzylhydrazine HCl, hydralazine HCl, clorgyline HCl, deprenyl HCl,L(-)-, deprenyl HCl,D(+)-, hydroxylamine HCl, iproniazid phosphate, 6-MeO-tetrahydro-9H-pyrido-indole, nialamide, pargyline HCl, quinacrine HCl, semicarbazide HCl, tranylcypromine HCl, N,N-diethylaminoethyl-2,2-diphenylvalerate hydrochloride, 3-isobutyl-1-methylxanthne, papaverine HCl, indomethacind, 2-cyclooctyl-2-hydroxy-

ethylamine hydrochloride, 2,3-dichloro-a-methylbenzylamine (DCMB), 8,9-dichloro-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride, p-aminoglutethimide, p-aminoglutethimide tartrate,R(+)-, p-aminoglutethimide tartrate,S(-)-, 3-iodotyrosine, alpha-methyltyrosine,L-, alpha -methyltyrosine,D L-, acetazolamide, dichlorphenamide, 6-hydroxy-2-benzothiazolesulfonamide, and allopurinol.

Neurotoxins are substances which have a toxic effect on the nervous system, e.g. nerve cells. Neurotoxins include adrenergic neurotoxins, cholinergic neurotoxins, dopaminergic neurotoxins, and other neurotoxins. Examples of adrenergic neurotoxins include N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride. Examples of cholinergic neurotoxins include acetylethylcholine mustard hydrochloride. Examples of dopaminergic neurotoxins include 6-hydroxydopamine HBr, 1-methyl-4-(2-methylphenyl)-1,2,3,6- tetrahydro-pyridine hydrochloride, 1-methyl-4-phenyl-2,3- dihydropyridinium perchlorate, N-methyl-4-phenyl-1,2,5,6- tetrahydropyridine HCl, 1-methyl-4-phenylpyridinium iodide.

Opioids are substances having opiate like effects that are not derived from opium. Opioids include opioid agonists and opioid antagonists. Opioid agonists include codeine sulfate, fentanyl citrate, hydrocodone bitartrate, loperamide HCl, morphine sulfate, noscapine, norcodeine, normorphine, thebaine. Opioid antagonists include nor-binaltorphimine HCl, buprenorphine, chlornaltrexamine 2HCl, funaltrexamione HCl, nalbuphine HCl, nalorphine HCl, naloxone HCl, naloxonazine, naltrexone HCl, and naltrindole HCl.

Hypnotics are substances, which produce a hypnotic effect. Hypnotics include pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures, thereof, heterocyclic hypnotics, dioxopiperidines, glutarimides, diethyl isovaleramide, a-bromoisovaleryl urea, urethanes and disulfanes.

Antihistamines are substances, which competitively inhibit the effects of histamines. Examples include pyrilamine, chlorpheniramine, tetrahydrazoline, and the like.

Lubricants are substances that increase the lubricity of the environment into which they are delivered. Examples of biologically active lubricants include water

and saline.

Tranquilizers are substances, which provide a tranquilizing effect. Examples of tranquilizers include chloropromazine, promazine, fluphenzaine, reserpine, deserpidine, and meprobamate.

Anti-convulsants are substances, which have an effect of preventing, reducing, or eliminating convulsions. Examples of such agents include primidone, phenytoin, valproate, Chk and ethosuximide.

Muscle relaxants and anti-Parkinson agents are agents which relax muscles or reduce or eliminate symptoms associated with Parkinson's disease. Examples of such agents include mephenesin, methocarbomal, cyclobenzaprine hydrochloride, trihexylphenidyl hydrochloride, levodopa/carbidopa, and biperiden.

Anti-spasmodics and muscle contractants are substances capable of preventing or relieving muscle spasms or contractions. Examples of such agents include atropine, scopolamine, oxyphenonium, and papaverine.

Miotics and anti-cholinergics are compounds, which cause bronchodilation. Examples include echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, epinephrine, neostigmine, carbachol, methacholine, bethanechol, and the like.

Anti-glaucoma compounds include betaxalol, pilocarpine, timolol, timolol salts, and combinations of timolol, and/or its salts, with pilocarpine.

Anti-parasitic, -protozoal and -fungals include ivermectin, pyrimethamine, trisulfapyrimidine, clindamycin, amphotericin B, nystatin, flucytosine, natamycin, and miconazole.

Anti-hypertensives are substances capable of counteracting high blood pressure. Examples of such substances include alpha-methyldopa and the pivaloyloxyethyl ester of alpha-methyldopa.

Analgesics are substances capable of preventing, reducing, or relieving pain. Examples of analgesics include morphine sulfate, codeine sulfate, meperidine, and nalorphine.

Anti-pyretics are substances capable of relieving or reducing fever and anti-inflammatory agents are substances capable of counteracting or suppressing inflammation. Examples of such agents include aspirin (salicylic acid),

indomethacin, sodium indomethacin trihydrate, salicylamide, naproxen, colchicine, fenoprofen, sulindac, diflunisal, diclofenac, indoprofen and sodium salicylamide.

Local anesthetics are substances, which have an anesthetic effect in a localized region. Examples of such anesthetics include procaine, lidocain, tetracaine and dibucaine.

Ophthalmics include diagnostic agents such as sodium fluorescein, rose bengal, methacholine, adrenaline, cocaine, and atropine. Ophthalmic surgical additives include alpha-chymotrypsin and hyaluronidase.

Prostaglandins are art recognized and are a class of naturally occurring chemically related, long-chain hydroxy fatty acids, which have a variety of biological effects.

Anti-depressants are substances capable of preventing or relieving depression. Examples of anti-depressants include imipramine, amitriptyline, nortriptyline, protriptyline, desipramine, amoxapine, doxepin, maprotiline, tranylcypromine, phenelzine, and isocarboxazide.

Anti-psychotic substances are substances, which modify psychotic behavior. Examples of such agents include phenothiazines, butyrophenones and thioxanthenes.

Anti-emetics are substances, which prevent or alleviate nausea or vomiting. An example of such a substance includes dramamine.

Imaging agents are agents capable of imaging a desired site, e.g. tumor, *in vivo*. Examples of imaging agents include substances having a label, which is detectable *in vivo*, e.g. antibodies attached to fluorescent labels. The term antibody includes whole antibodies or fragments thereof.

Specific targeting agents include agents capable of delivering a therapeutic agent to a desired site, e.g. tumor, and providing a therapeutic effect. Examples of targeting agents include agents which can carry toxins or other agents which provide beneficial effects. The targeting agent can be an antibody linked to a toxin, e.g. ricin A or an antibody linked to a drug.

Neurotransmitters are substances that are released from a neuron on excitation and travel to either inhibit or excite a target cell. Examples of neurotransmitters include dopamine, serotonin, q-aminobutyric acid, norepinephrine, histamine, acetylcholine, and epinephrine.

Cell response modifiers are chemotactic factors such as platelet-derived growth factor (PDGF). Other chemotactic factors include neutrophil-activating protein, monocyte chemoattractant protein, macrophage-inflammatory protein, platelet factor, platelet basic protein, and melanoma growth stimulating activity; epidermal growth factor, transforming growth factor (alpha), fibroblast growth factor, platelet-derived endothelial cell growth factor, insulin-like growth factor, nerve growth factor, and bone growth/cartilage-inducing factor (alpha and beta), or other bone morphogenetic protein.

Other cell response modifiers are the interleukins, interleukin inhibitors or interleukin receptors, including interleukin 1 through interleukin 10; interferons, including alpha, beta and gamma; hematopoietic factors, including erythropoietin, granulocyte colony stimulating factor, macrophage colony stimulating factor and granulocyte-macrophage colony stimulating factor; tumor necrosis factors, including alpha and beta; transforming growth factors (beta), including beta-1, beta-2, beta-3, inhibin, and activin; and bone morphogenetic proteins.

The aspected particle may be incorporated into a variety of architecture in order to obtain the desired release profiles. Exemplary fabrication methods and drug delivery vehicle architectures include the following.

Aspected particles may be prepared according to conventional methods. For example, the drug and pharmaceutically acceptable excipients may be taken up into solution or may be made into a slurry. The solution or slurry may be cast against a flat surface and allowed to dry into a thin film. The film may be further cut or shredded into aspected particles of the desired dimensions. The films may be formed by air-drying, oven-drying, lyophilization and the like.

In another embodiment of the invention, the drug and pharmaceutically acceptable excipients may be taken up into a liquid to form a paste or dough-like mixture. The mixture may be forced through a screen having the appropriate dimensions. The resulting particles may be dried as described hereinabove. The drug may be incorporated the aspected particles by microgranulation of the drug with suitable pharmaceutically acceptable excipients and then mixing the microgranulars with another bases and coating polymers to form aspected particles and processing the mixture as described herein.

In another embodiment of the invention, the particles may be prepared using a spray drying technique (batch process). A drug solution (1 μg/mL - 5 mg/mL) containing acceptable pharmaceutical excipients may be sprayed on a rotating drum. The drum could be either warm or cooled to subambient. The system could be under reduced pressure (al these parameters are determined by the drug solubility and solvent volatility).

Particle size may be controlled by mechanical milling or cryomilling to reduce the solid mixture to the desired size (1 μm to 7 mm). The preferred range is 1 to 1000 μm, and more preferably 10 - 500 μm. The particles may be used as is or may be fractionated to the desired size distribution using mechanical screens. The desired fractions may be coated with a single or double coating using a Worster Coater. In preferred embodiments, the first coat could be a time release coat while the second coat could provide a slip, a taste masking, a moisture barrier.

Milling of aspected particles may be accomplished using acceptable pharmaceutical processes. Thus, for example, the particles may be compressed between two rollers (when wet) followed by drying to form aspected particles.

In another embodiment of the invention, the aspected particles may be manufactured in a continuous process by spraying a polymeric solution containing the drug and optional excipients onto a moving belt (heated or cooled) to form a thin film, which can be dried and cut into particles. Alternatively, the process may be used to form laminate structures, for example, by first spray coating a film-forming layer, then applying a drug solution to the dried coating layer (in a non-miscible solvent for the coating layer). Thereafter, a final layer may be sprayed on to form a three-laminated product.

The film mono- or multi-laminate sheet may be reduced in size by mechanical mill or cryomill and blended to form uniform aspected particles (1 μm to 10 mm). Further, the aspected particles may be coated as described above to cover edges and/or to add additional desired properties such as to provide a slip, a taste masking or a moisture barrier

In another embodiment of the invention, a liquid may be frozen to form the aspected particle. A cylindrical evaporator with a refrigerant circulation tubing

assembly between its inner and outer surfaces and having an axially driven rotatable shaft in the evaporator center is used. A nozzle on the shaft discharges liquid toward the evaporator inner surface, where it freezes as a sheet; and a blade on the shaft removes the frozen sheet as flakes.

A pharmaceutical preparation may be prepared free of organic solvents for oral administration which contains a meltable active ingredient for a delayed release of the meltable active ingredient and which includes forming a mixture consisting of the meltable active ingredient and a matrix forming auxiliary agent which is meltable and soluble in the active ingredient when the active ingredient is melted; melting the mixture; and kneading the melt until a homogeneous uniform mass is obtained; and forming aspected microparticulates by rolling between rotating drums and mincing the sheet.

The aspected particles of the invention may also be prepared by extruding single or multi-layered thin films **30** incorporating the drug which is then shredded into aspected particles as illustrated in Figure 3A. The multi-layer laminated form contains a core layer **32** in which at least a major portion of the medicament is contained. The core layer consists is flanked by layers **34** containing either water-soluble polymers, water-insoluble polymers, or both, in order to obtain the desired release kinetics. The laminate aspected particle may also contain an outer protective-barrier membrane layer (not shown). Alternatively, the laminate particle may be made up of layers in which each has a difference composition, as shown in Figure 3B. This film is treated is shredded as previously described.

Aspected particles may be formulated as capsules, tablets or powders that may be added to water or other suitable liquid. The particles remain suspended in the liquid so that administration of the drug is accomplished as a drink, avoiding difficulties of swallowing or chewing tablets, or parenteral administration and therefore improving patient compliance. The aspected particles form a fine suspension in water before ingestion, reducing effects of food, presence of bile, and pH, especially on dissolution of sparingly soluble drugs. They prevent absorption in the oral cavity, and allow targeting of drug release at the required absorption site. Drug release can be controlled as described herein to give a therapeutic effect over a any desired time period, e.g., a 24-hour period for a once a day administration.

In the fabrication of fast-dissolving tablets, aspected particles may be incorporated into an effervescent matrix that dissolves in the mouth with or without additional water. The aspected particles then become available and slide easily down to the esophagus. Each aspected particle becomes a sustained release reservoir. Current fast dissolving tablet technologies provide just immediate release and do not provide added benefits as for sustained release capabilities. See, for Example U.S. Patent No. 4,581,232. Alternatively, aspected particles may be formulated into capsules, tablets or powders that could be effervesce on addition of water or form suspensions once added to water (or juice).

In the fabrication of chewable tablets, aspected particles are incorporated into a tablet that could be chewed. Once chewed, the particles become available and slide easily down to the esophagus. Each aspected particle may function as a sustained release reservoir.

In other preferred embodiments, a composition is providing comprising a combination of sustained and rapid release. In one embodiment, aspected particulate formulations may be provided for once-daily oral administration in which the drug is formulated in aspected particle designed to release the drug at a rate such that therapeutically effective blood levels are maintained over 24 hours. The formulation includes a second portion formulated for prompt release to obtain a rapid therapeutic response.

Alternatively, a single particle could be made of a combination of fast and slow release. As an example, an aspected microparticulate comprising: (a) a core of drug or its salt, and an acceptable excipients surrounded by (b) a membrane, containing mostly a water insoluble, film forming synthetic polymers, with a minor amounts of water soluble synthetic polymers; and (c) a final layer of a rapid release form of drug, to provide effective therapeutic amounts immediate after administration.

In another embodiment of the invention an oral formulation for controlled absorption of drugs comprises aspected particulate having (1) a core **40** containing the drug, or its pharmaceutically acceptable salt, and (2) a membrane **42** of at least one film-forming polymer which controls the rate of the drug release into an aqueous medium, as is shown in Figure 4. The aspected microparticulate also could have a

pH-independent dissolution rate.

In another embodiment of the invention, an oral formulation controlled absorption of drugs comprises aspected microparticles having (1) a core **50** of swellable hydrogel that swells in response to stimuli or water, (2) a drug **52** or its pharmaceutically acceptable salt, and (3) a membrane **54** of at least one film-forming polymer which controls the rate of the drug release into an aqueous medium. The swellable hydrogel core will assist to push out the drug payload **56** in a controlled fashioned through the coating, as is illustrated in Figure 5.

In yet another embodiment of the invention, an oral formulation includes a swellable hydrogel, that swells in response to stimuli or water, located in the core of the aspected particle. The core swells in response to stimuli in order to prevent the decrease in the release rate towards the end of the diffusion process of the drug to the environment. The swellable gel core may be used in aspected particles with or without an outer coating used to promote mouth-feel or control drug delivery. It may also be used in aspected particles described above having a membrane of a film-forming polymer which controls the rate of release into an aqueous medium

Once the aspected particles pass the mouth, it may disintegrate in the stomach or gastrointestinal tract to the individual aspected or spherical granulars to increase the distribution over a wide surface area in the gastrointestinal tract. Poorly water-soluble drugs could be incorporated into polymeric films that could be manufactured into aspected particles. For example, polymers such as hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose phthalate, poloxamers or polyethyleneglycols (PEG). The drug could be solubilized or suspended in those polymers. One optional drug state would be of an amorphous state to enhance drug stability and drug solubility. In another method the drug could be crystalline and each crystal is coated separately. Disintegrants could be added to the aspected particle to precisely control the release kinetics. The disintegrants control the water uptake to a hydrophobic matrix and as a result effect the coating of the particle.

The aspected particle could be constructed from multilayers, as shown in Figure 3. Where some layers contain drug and some layers may not contain drugs. The drug will release through the non-drug layers that will act to control the release

barriers. It would also allow the incorporation of a few different drugs into one particle in different layers. In other embodiments, the aspected particle could be constructed by forming an inner, inert core, as shown in Figure 5. Followed by coating the inner core with active pharmaceutical agent. Finally the unit is coated with another layer that could act as taste masking layer and or to control the release layer.

A sustained-release aspected particle includes an excipient or coating; and at least one pH adjuster selected from organic acid, organic acid salt, organic base, inorganic base and base salt. The excipient or coating composition surrounds a core comprising a medicament whose solubility varies with pH. The pH of the excipient or coating composition is adjusted to a desired pH to ensure that the rate of dissolution of the medicament is independent of the pH of the environment in which dissolution occurs.

A time-controlled explosion system in which drug release is caused by explosion of a membrane after a definite time period, said system comprising a preparation in the form of a aspected particles, said preparation comprising a core, a drug, swelling agent and an outer membrane of water-insoluble coating material.

Oral pharmaceutical preparations of aspected particles, which comprise a pharmacologically active drug, bound to small particles of an ion-exchange resin to provide a drug-resin complex having a drug content above a specified value. The drug-resin complex is subsequently coated with a water-permeable diffusion barrier coating that is insoluble in gastrointestinal fluids thereby providing a controllable sustained release of drug under conditions encountered in the gastrointestinal tract.

It is anticipated that the aspected particle may be used in conjunction with a wide variety of drugs. In particular, the aspected particle may be used in the controlled abortion of methyldopa. The aspected particle comprises (a) an aspected particle having a core of methyldopa (or its pharmaceutical salt) and an organic acid; and (b) a membrane or coating surrounding the core mainly comprising a pharmaceutically acceptable, film-forming, water-insoluble polymer. By controlling the number of coating layers permit a controlled release of methyldopa from the pellet. Rate of release over 24 hours after oral administration and is pH independent.

In another embodiment, the aspected particle is adapted to deliver ditiazem. A controlled absorption ditiazem formulation for oral administration includes aspected particles having a core of ditiazem or a its pharmaceutically acceptable salts. A membrane(s) or coating surrounds the core and contains a major amount of a pharmaceutically acceptable film-forming, water-insoluble polymer and a minor amount of a pharmaceutically acceptable film-forming, water-soluble polymer, the number of layers in the membrane and the ratio of the water soluble polymer to water-insoluble polymer being effective to permit release of the ditiazem from the aspected particle at a rate allowing controlled absorption thereof for 12 to 24 hours period following oral administration.

In another embodiment of the invention, an oral deliver vehicle is provided for delivery of verapamil. The formulation includes aspected particles consisting of a core including verapamil and a surrounding membrane or coating consisting mainly of pharmaceutically acceptable, film-forming water-insoluble polymer plus a small amount of a similar water-soluble polymer. The number of layers and the ratio of the water-soluble to water-insoluble polymers in the coating is chosen so that the drub is released at a rate which allows controlled absorption over 24 hr following oral administration, the preferred rate being measured *in vivo* would be T_{max} of 7-10 hr.

The aspected particles may be provided in the form of a gelatin capsule (or similar structure) so that the dosage form could be taken either as a whole or be opened and poured onto food or drink. The packaging may be designed to enhance the ease of opening, a feature particularly attractive to an aging patient population. By way of example, the aspected particles may be provided in a sachet. Thus, a single packaging design of the aspected particles, i.e., a capsule, may be either ingested as an intact capsule or opened and administered as an additive in liguids or other suitable bases.

In yet a further example of the invention, an oral drug delivery vehicle for administering includes a sealable container including a removable seal for holding and storing a desired dose of the pharmaceutically active agent as an aspected particle in a stable condition until needed and a base which is sweetened, flavored and colored to produce a mixture that is palatable and pleasing to the taste. The

mixture and the aspected particles are sealed inside the container. The medication is in a aspected particle form and a delivery medium are stored in a chambered container separated by a rupturable membrane which is ruptured to mix the container contents.

These an other embodiments of the invention are illustrated by way of the examples which are provided for the purpose of illustration only and which are not intended to be limiting of the invention.

Example 1. L-DOPA (Sigma, Lot 55H0565, 1.01 g); sucrose (2.04 g) and purified water (E-Pure, 1.5g) were mixed together. The semisolid mixture was stirred until it became homogeneous and spread on a glass plate and dried at 70 °C overnight. The product was ground to particles of roughly 1 X 1 X 0.1 mm in dimensions. Half of these particles were dipped in 4% solution of ethylcellulose (Benecel) in methyl alcohol (Malinkrodt, Lot 3016KVRG) and air dried.

The aspected particles were placed in phosphate buffer saline solution, pH 7.4 at 37 °C and the solution was analyzed at given time points for the presence of L-DOPA by UV at 287 nm. We obtained an almost linear release of the L-DOPA over 24 hours. There was minimal difference in the release kinetics between the coated and the non-coated aspected particles. In this example the water soluble excipient (sucrose) influenced the release kinetics of the water insoluble drug.

Example 2. L-Dopa (Sigma, Lot 55H0565, 0.2089 g); ethylcellulose (Benecel, Hercules, Lot FP10 13415), 0.3009 g); Avicel (FMC, Lot M723C, 0.4996 g) and purified water (E-Pure) were mixed together. The semisolid mixture was stirred until it became homogeneous and was spread on a glass plate and dried at 70 °C for 4 hours. The product was cut to small square aspected particles of roughly 1 X 1 X 0.1 mm in dimensions. Half of these particles were dipped in 4% solution of ethylcellulose (Benecil) in methyl alcohol (Malinkrodt, Lot 3016KVRG) and dried.

The aspected particles were placed in phosphate buffer saline solution pH 7.4 at 37 °C and were analyzed at given time points for the release of L-DOPA by UV at 287 nm. We obtained a zero order release kinetics for the L-Dopa over 24 hours. The coated particles released 26% of the incorporated L-Dopa while the non-coated particles released 76% of the incorporated L-Dopa over that time period. In this example the water insoluble excipient influenced the release kinetics of the water

insoluble drug and the kinetics was further affected by the coating.

Example 3 Benecel (Hercules, Lot FP10 1345, 0.57 g), Avicel (FMC, Lot M723C, 0.81 g), Magnesium stearate (Malinkrodt, Lot 2256KVKD, 0.13 g) were mixed and purified water (4.9g) was added to form a dough-like mixture. The resulting semi-solid was spread into a screen with 1 X 1 mm opening and placed in a 65 °C oven for 1 h. The dried solid was pushed from the screen to form aspected particles. These particles were divided into three parts: 1/3 of the particles were left as is; 1/3 were coated with a 1.4% Carbopol® solution (poly(acrylic acid), BF Goodrich, Lot CC769F88704) containing 1.4% banana flavor (Frontier); and 1/3 were coated with 1.3% Carbopol solution containing 1% PEG 600 (Union Carbide, Lot IS781428) and 1.4% banana favor. The particles were blind-tasted for their organoleptic feel: the uncoated group felt hard and gritty; the Carbopol coated particles were a bit hard initially and become lubricious; the particles coated with both Carbopol and PEG were lubricious and pleasant tasting from the start. In this example the coating with fast swelling hydrogel improved the organoleptic feel of the aspected particle.

Example 4 Phenylpropanolamine (Sigma, Lot 75F0551, 0.20 g); ethylcellulose (Benecel, Hercules, Lot FP10 13415), 0.30 g); Avicel (FMC, Lot M723C, 0.36 g) and magnesium stearate (Millinckrodt, Lot 2256KVKD, 0.01g) were mixed to form a homogeneous solid mixture. Purified water (E-Pure, 2.1 g) was added and mixed together to form a dough like consistency. The semisolid mixture was spread on a glass slide and freeze dried overnight. The dry product was cut to small square aspected particles of 2 X 2 X 0.1 mm in dimensions. 1/2 of these particles were dipped in 0.3% solution of ethylcellulose (Benecil) in methyl alcohol (Malinkrodt, Lot 3016KVRG) and ½ left as is.

The aspected particles were placed in phosphate buffer saline solution pH 7.4 at 37 °C and were analyzed at given time points for the release of Phenylpropanolamine by UV at 256 nm. In this example the coating retarded the release of a highly water soluble drug phenylpropanolamine.

Particle	$t_{50\%}$	$t_{100\%}$
Uncoated	-	50 min
Coated particles	1 h	8 h

What is claimed is:

1. An oral delivery vehicle, comprising:

an aspected particle including a pharmaceutically active component and excipients, wherein the vehicle is formulated and/or constructed and arranged to provide controlled delivery of the pharmaceutically active component.

2. An oral delivery vehicle, comprising:

an aspected particle including a pharmaceutically active component and excipients, the aspected particle having one dimension that is about an order of magnitude smaller than the other two dimensions.

3. An oral delivery vehicle with an acceptable mouth-feel, comprising:

an aspected particle including a pharmaceutically active component and excipients, the aspected particle having one dimension that is about an order of magnitude smaller than the other two dimensions; and

a lubricious coating on the particle.

4. The delivery vehicle of claim 1, wherein controlled delivery is attained by coating the particle.

5. The delivery vehicle of claim 4, the coating is selected as a diffusion barrier to control drug delivery.

6. The delivery vehicle of claim 4, wherein the coating is selected as a barrier being impermeable to diffusion under a first set of environmental conditions, and permeable to diffusion under a second set of environmental conditions.

7. The delivery vehicle of claim 6, wherein the environmental condition is selected from the group consisting of temperature, pH, ionic strength and particular molecules.

8. The delivery vehicle of claims 1, 2 or 3, further comprising

a base having a consistency capable of being spoon-fed and capable of ingestion

by a patient, the delivery vehicle being disposed therein.

9. The oral delivery vehicle of claim 8, wherein the base may be food or non-food.

10. The oral delivery vehicle of claim 8, further comprising:

a sealable container including a removable seal for holding and storing the aspected particles in a stable condition until needed, wherein the aspected particles and the base are sealed inside the container.

11. The oral deliver vehicle of claim 8, wherein the base is sweetened, flavored and colored to produce a base that is palatable and pleasing to the taste.

12. The delivery vehicle of claim 3, wherein the lubricious coating is a hydrophobic coating.

13. The delivery vehicle of claim 12, wherein the hydrophobic coating is selected from the group consisting of silicone oils, siloxanes and ethyl acetate.

14. The delivery vehicle of claim 3, wherein the coating is a hydrophilic coating.

15. The delivery vehicle of claim 14, wherein the hydrophilic coating is selected from the group consisting of polyvinyl alcohols (PVA), polyvinylpyrrolidone (PVP), polyacrylic acids (PAA), poly(N-vinyl lactams), polyethylene oxides, polyvinyl ethers and derivatives thereof.

16. The delivery vehicle of claim 3, wherein the coating swells to become lubricious in the presence of an aqueous medium.

17. The delivery vehicle of claim 1, further comprising;

a lubricious coating on the outer surface of the aspected particle selected to

enhance mouth-feel.

18. The oral delivery vehicle of claim 1, wherein the controlled drug delivery is attained by selection of appropriate excipients.

19. The oral delivery vehicle of claim 1, wherein the aspected particle is a laminate structure having a core layer comprised of the pharmaceutically active component and outer layers selected to control the delivery of the component from the core layer.

20. The oral delivery vehicle of claim 19, further comprising:

a lubricious coating on the outer surface of the aspected particle selected to enhance mouth-feel.

21. The oral delivery vehicle of claim 1, wherein the aspected particles are incorporated into a tablet, capsule, fast dissolving tablet or chewable tablet.

22. The oral deliver vehicle of claim 1, wherein the aspected particles are incorporated into a capsule configured and arranged to permit opening of the capsule prior to administration to a patient.

Figure 1

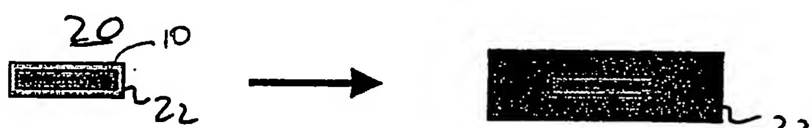

Figure 2

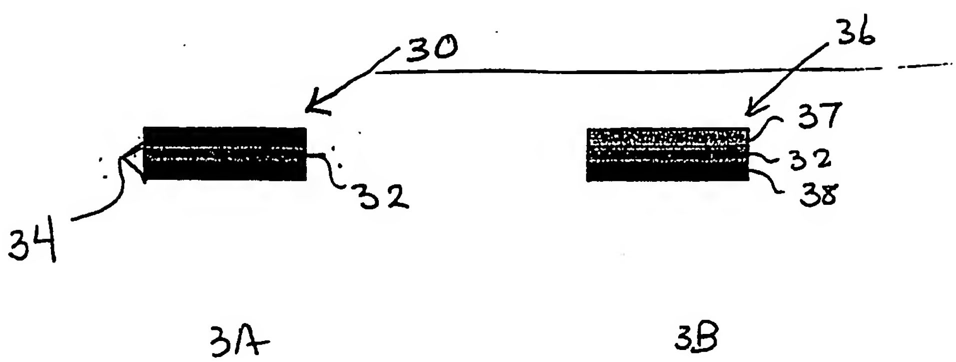

Figure 3.

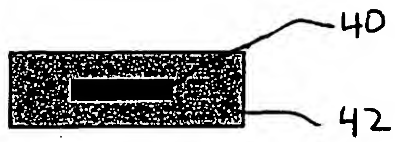

Figure 4

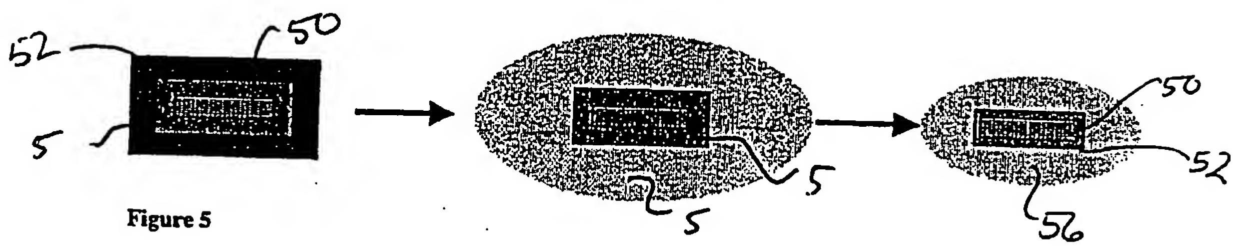

Figure 5